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L3: Entry 1 of 1 File: USPT

DOCUMENT-IDENTIFIER: US 5998205 A
TITLE: Vectors for tissue-specific replication

US PATENT NO. (1):
5998205

Brief Summary Text (12):
The organization of the adenovirus genome is similar in all of the adenovirus groups and specific functions are generally positioned at identical locations for each serotype studied. Early cytoplasmic messenger RNAs are complementary to four defined, noncontiguous regions on the viral DNA. These regions are designated (E1-E4). The early transcripts have been classified into an array of immediate early (E1a), delayed early (E1b, E2a, E2b, E3 and E4), and intermediate (IVa2.1X) regions.

Brief Summary Text (13):
The E1a region is involved in transcriptional transactivation of viral and cellular genes as well as transcriptional repression of other sequences. The E1a gene exerts an important control function on all of the other early adenovirus messenger RNAs. In normal tissues, in order to transcribe regions E1b, E2a, E2b, E3, or E4 efficiently, active E1a product is required. However, as discussed below, the E1a function may be bypassed. Cells may be manipulated to provide E1a-like functions or may naturally contain such functions. The virus may also be manipulated to bypass the functions as described below.

Brief Summary Text (23):
However, 293 cells are subject to severe limitations as producer cells for adenovirus vectors. Growth rates are low. Titres are limited, especially when the vector produces a heterologous gene product that proves toxic for the cells. Recombination with the viral E1 sequence in the genome can lead to the contamination of the recombinant defective virus with unsafe wild-type virus. The quality of certain viral preparations is poor with regard to the ratio of virus particle to plaque forming unit. Further, the cell line does not support growth of more highly deleted mutants because the expression of E1 in combination with other viral genes in the cellular genome (required to complement the further deletion), such as E4, is toxic to the cells. Therefore, the amount of heterologous DNA that can be inserted into the viral genome is limited in these cells. It is desirable, therefore, to produce adenovirus vectors for gene therapy in a cell that cannot produce wild-type recombinants and can produce high titres of high-quality virus. The present invention overcomes these limitations.

Detailed Description Text (25):
In alternative embodiments, adenovirus vectors are provided with any of the other genes essential for replication, such as E2-E4, under control of a heterologous transcriptional regulatory sequence.

CLAIMS:

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for the replication of said vector, wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector, wherein said transcriptional regulatory sequence functions in said cell so that replication of

the vector occurs in said cell, wherein said coding region is selected from the group consisting of E1 a E1b, and E2 and E4 coding regions.

a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said virion, wherein said transcriptional regulatory sequence functions in said cell so that replication of the virion occurs in said cell wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

=> d his

(FILE 'HOME' ENTERED AT 17:31:06 ON 14 AUG 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 17:31:20 ON 14 AUG 2002

L1 80946 S ADENOVIRUS
L2 5006 S APOPTOSIS AND L1
L3 769 S ADENOVIRUS(8A)(INDUC? OR STIMULAT? OR PROMOT?)(5A)APOPTOSIS
L4 12437 S E-4
L5 0 S L3 AND L4
L6 308 DUP REM L3 (461 DUPLICATES REMOVED)

=> d au ti so 250-308 l6

L6 ANSWER 250 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Lill, Nancy L.; Grossman, Steven R.; Ginsberg, Doron; DeCaprio, James; Livingston, David M.
TI Binding and modulation of p53 by p300/CBP coactivators
SO Nature (London) (1997), 387(6635), 823-827
CODEN: NATUAS; ISSN: 0028-0836

L6 ANSWER 251 OF 308 MEDLINE DUPLICATE 151
AU Maxwell S A; Capp D; Acosta S A
TI Telomerase activity in immortalized endothelial cells undergoing p53-mediated apoptosis.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Dec 29) 241 (3)
642-5.
Journal code: 0372516. ISSN: 0006-291X.

L6 ANSWER 252 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Hayakawa, Yoichi
TI Screening for microbial metabolites which induce apoptosis selectively against cancer cells
SO Nippon Nogei Kagaku Kaishi (1997), 71(5), 520-522
CODEN: NNKKAA; ISSN: 0002-1407

L6 ANSWER 253 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE 152
AU Branton, Philip E. (1); Querido, Emmanuelle
TI Human adenoviruses: Windows on apoptosis and cancer.
SO M-S (Medecine Sciences), (1997) Vol. 13, No. 4, pp. 492-500.
ISSN: 0767-0974.

L6 ANSWER 254 OF 308 MEDLINE DUPLICATE 153
AU Seth P; Katayose D; Li Z; Kim M; Wersto R; Craig C; Shanmugam N; Ohri E; Mudahar B; Rakkar A N; Kodali P; Cowan K
TI A recombinant **adenovirus** expressing wild type p53 **induces apoptosis** in drug-resistant human breast cancer cells: a gene therapy approach for drug-resistant cancers.
SO CANCER GENE THERAPY, (1997 Nov-Dec) 4 (6) 383-90.
Journal code: 9432230. ISSN: 0929-1903.

L6 ANSWER 255 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Derrow, Sol; Wojno, Kirk J.; Pearsall, Carolyn; Charles, Linda; Montie, James E.; Clarke, Michael; Sandra, Martin G.
TI **Apoptosis induction** by **adenovirus**-BCLX-S: A rational strategy for bladder cancer gene therapy.

SO Journal of Urology, (1997) Vol. 157, No. 4 SUPPL., pp. 310.
Meeting Info.: 92nd Annual Meeting of the American Urological Association New Orleans, Louisiana, USA April 12-17, 1997
ISSN: 0022-5347.

L6 ANSWER 256 OF 308 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 154
AU Zeng, Yi-Xin; Prabhu, Nita S.; Meng, Ray; El-Deiry, Wafik S.
TI Adenovirus-mediated p53 gene therapy in nasopharyngeal cancer
SO International Journal of Oncology (1997), 11(2), 221-226
CODEN: IJONES; ISSN: 1019-6439

L6 ANSWER 257 OF 308 MEDLINE DUPLICATE 155
AU Jones D L; Thompson D A; Munger K
TI Destabilization of the RB tumor suppressor protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis.
SO VIROLOGY, (1997 Dec 8) 239 (1) 97-107.
Journal code: 0110674. ISSN: 0042-6822.

L6 ANSWER 258 OF 308 MEDLINE DUPLICATE 156
AU Yamashita T; Yamano S; Fujinaga K
TI **Induction** and suppression of **apoptosis** by **adenovirus** genes.
SO UIRUSU, (1997 Jun) 47 (1) 77-87. Ref: 78
Journal code: 0417475. ISSN: 0042-6857.

L6 ANSWER 259 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Watanabe, Miho; Shirayoshi, Yasuaki; Koshimizu, Uichi; Hashimoto, Shuichi;
Yonehara, Shin; Eguchi, Yutaka; Tsujimoto, Yoshihide; Nakatsuji, Norio
TI Gene transfection of mouse primordial germ cells in vitro and analysis of their survival and growth control
SO Experimental Cell Research (1997), 230(1), 76-83
CODEN: ECREAL; ISSN: 0014-4827

L6 ANSWER 260 OF 308 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 157
AU Lefkovits, Ivan; Su, Zao-Zhong; Fisher, Paul B.; Grunberger, Dezider
TI Caffeic acid phenethyl ester profoundly modifies protein synthesis profile
in type 5 adenovirus-transformed cloned rat embryo fibroblast cells
SO International Journal of Oncology (1997), 11(1), 59-67
CODEN: IJONES; ISSN: 1019-6439

L6 ANSWER 261 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Li, Hewei (1); Lochmuller, Hanns (1); Seth, Prem; Karpati, George (1); Nalbantoglu, Josephine (1)
TI Gene therapy of malignant gliomas: **Adenovirus**-mediated wild-type p53 expression **induces** widespread **apoptosis** of human glioma cells independently of endogenous p53 status.
SO Neurology, (1997) Vol. 48, No. 3 SUPPL. 2, pp. A34.
Meeting Info.: 49th Annual Meeting of the American Academy of Neurology Boston, Massachusetts, USA April 12-19, 1997
ISSN: 0028-3878.

L6 ANSWER 262 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Derrow, S.; Wojno, K.; Pearsall, C.; Charles, L.; Montie, J.; Clarke, M.; Sanda, M. G.
TI **Apoptosis induction** by **adenovirus**-bclx-s: A rational strategy for bladder cancer gene therapy.
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 11.

Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.

L6 ANSWER 263 OF 308 MEDLINE DUPLICATE 158
AU Nakajima T; Morita K; Ohi N; Arai T; Nozaki N; Kikuchi A; Osaka F; Yamao F; Oda K
TI Degradation of topoisomerase IIalpha during **adenovirus** E1A-**induced apoptosis** is mediated by the activation of the ubiquitin proteolysis system.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 4) 271 (40) 24842-9.
Journal code: 2985121R. ISSN: 0021-9258.

L6 ANSWER 264 OF 308 MEDLINE DUPLICATE 159
AU Chen G; Branton P E; Yang E; Korsmeyer S J; Shore G C
TI Adenovirus E1B 19-kDa death suppressor protein interacts with Bax but not with Bad.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Sep 27) 271 (39) 24221-5.
Journal code: 2985121R. ISSN: 0021-9258.

L6 ANSWER 265 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Moore, Mary; Horikoshi, Nobuo; Shenk, Thomas
TI Oncogenic potential of the adenovirus E4orf6 protein
SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(21), 11295-11301
CODEN: PNASA6; ISSN: 0027-8424

L6 ANSWER 266 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Gao, Guang-Ping; Yang, Yiping; Wilson, James M.
TI Biology of adenovirus vectors with E1 and E4 deletions for liver-directed gene therapy
SO Journal of Virology (1996), 70(12), 8934-8943
CODEN: JOVIAM; ISSN: 0022-538X

L6 ANSWER 267 OF 308 MEDLINE DUPLICATE 160
AU Marcellus R C; Teodoro J G; Wu T; Brough D E; Ketner G; Shore G C; Branton P E
TI Adenovirus type 5 early region 4 is responsible for E1A-induced p53-independent apoptosis.
SO JOURNAL OF VIROLOGY, (1996 Sep) 70 (9) 6207-15.
Journal code: 0113724. ISSN: 0022-538X.

L6 ANSWER 268 OF 308 MEDLINE DUPLICATE 161
AU Whalen S G; Marcellus R C; Barbeau D; Branton P E
TI Importance of the Ser-132 phosphorylation site in cell transformation and **apoptosis induced** by the **adenovirus** type 5 E1A protein.
SO JOURNAL OF VIROLOGY, (1996 Aug) 70 (8) 5373-83.
Journal code: 0113724. ISSN: 0022-538X.

L6 ANSWER 269 OF 308 SCISEARCH COPYRIGHT 2002 ISI (R)
AU ROTA R (Reprint); CIRIELLI C; BLASI M A; MARTINOTTI S; TONIATO E; CAPOGROSSI M; PROCOPIO A; BALESTRAZZI E
TI **ADENOVIRUS**-MEDIATED WILD-TYPE P53 GENE-TRANSFER **INDUCES APOPTOSIS** AND INHIBITS PROLIFERATION OF HUMAN UVEAL MELANOMA-CELLS
SO INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (15 FEB 1996) Vol. 37, No. 3, pp. 5187.
ISSN: 0146-0404.

L6 ANSWER 270 OF 308 MEDLINE
AU Nakajima T
TI Degradation of topoisomerase II alpha precedes nuclei degeneration during **adenovirus** E1A-**induced apoptosis** and is mediated by the activation of the ubiquitin dependent proteolysis system.
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1996 Jul) 54 (7) 1828-35. Ref: 10
Journal code: 0420546. ISSN: 0047-1852.

L6 ANSWER 271 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Rota, R. (1); Cirielli, C.; Blasi, M. A. (1); Martinotti, S.; Toniato, E.; Capogrossi, M.; Procopio, A.; Balestrazzi, E. (1)
TI **Adenovirus**-mediated wild-type p53 gene transfer **induces apoptosis** and inhibits proliferation of human uveal melanoma cells.
SO Investigative Ophthalmology & Visual Science, (1996) Vol. 37, No. 3, pp. S1131.
Meeting Info.: 1996 Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 21-26, 1996
ISSN: 0146-0404.

L6 ANSWER 272 OF 308 MEDLINE DUPLICATE 162
AU Slack R S; Belliveau D J; Rosenberg M; Atwal J; Lochmuller H; Aloyz R; Haghighi A; Lach B; Seth P; Cooper E; Miller F D
TI **Adenovirus**-mediated gene transfer of the tumor suppressor, p53, **induces apoptosis** in postmitotic neurons.
SO JOURNAL OF CELL BIOLOGY, (1996 Nov) 135 (4) 1085-96.
Journal code: 0375356. ISSN: 0021-9525.

L6 ANSWER 273 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Nakajima, Takuma; Morita, Kenichi; Ohi, Naoto; Arai, Takao; Nozaki, Naohito; Kikuchi, Akihiko; Ohsaka, Fumio; Yamao, Fumiaki; Oda, Kinichiro
TI Degradation of topoisomerase II-alpha during **adenovirus** E1A-**induced apoptosis** is mediated by the activation of the ubiquitin proteolysis system.
SO Biochemical Society Transactions, (1996) Vol. 24, No. 4, pp. 565S.
Meeting Info.: 4th International Union of Biochemistry and Molecular Biology Conference Edinburgh, Scotland, UK July 14-17, 1996
ISSN: 0300-5127.

L6 ANSWER 274 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Boulakia, Charles A.; Chen, Gang; Ng, Florence WH; Teodoro, Jose G.; Branton, Philip E.; Nicholson, Donald W.; Poirier, Guy G.; Shore, Gordon C.
TI Bcl-2 and adenovirus E1B 19 kDa protein prevent E1A-induced processing of CPP32 and cleavage of poly(ADP-ribose) polymerase
SO Oncogene (1996), 12(3), 529-35
CODEN: ONCNES; ISSN: 0950-9232

L6 ANSWER 275 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Marinacci, M. (1); Giuliano, M. (1); Messina, E. (1); Capogrossi, M. C.; Cirielli, C.; Pass, H. I.; Modesti, A. (1); Carbone, M.; Procopio, A. (1)
TI **Adenovirus**-mediated wild-type p53 gene transfer **induces apoptosis** and inhibits in vivo tumor growth of human mesothelioma cells.
SO Journal of Investigative Medicine, (1996) Vol. 44, No. 3, pp. 280A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American

Federation for Clinical Research: Biomedicine '96, Medical Research from Bench to Bedside Washington, D.C., USA May 3-6, 1996
ISSN: 1081-5589.

L6 ANSWER 276 OF 308 SCISEARCH COPYRIGHT 2002 ISI (R)
AU GIULIANO M (Reprint); MARINACCI; MESSINA E; CAPOGROSSI M C; CIRIELLI C; PASS H I; MODESTI A; CARBONE M; PROCOPIO A
TI **ADENOVIRUS**-MEDIATED WILD-TYPE P53 GENE-TRANSFER **INDUCES APOPTOSIS** AND INHIBITS IN-VIVO TUMOR-GROWTH OF HUMAN MESOTHELIOMA CELLS
SO JOURNAL OF INVESTIGATIVE MEDICINE, (MAR 1996) Vol. 44, No. 3, pp. A280.
ISSN: 1081-5589.

L6 ANSWER 277 OF 308 CAPLUS COPYRIGHT 2002 ACS
IN Dedieu, Jean-Francois; Le, Roux Aude; Perricaudet, Michel
TI Adenovirus expression vectors using tumor-inducible expression cassettes for gene therapy in cancers
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2

L6 ANSWER 278 OF 308 CAPLUS COPYRIGHT 2002 ACS
IN Cotten, Matthew; Baker, Adam
TI Transformation of higher eukaryotic cells with genes encoding toxic gene products and prevention of toxic effects to achieve long-term gene expression
SO Ger. Offen., 25 pp.
CODEN: GWXXBX

L6 ANSWER 279 OF 308 MEDLINE DUPLICATE 163
AU Clarke M F; Apel I J; Benedict M A; Eipers P G; Sumantran V; Gonzalez-Garcia M; Doedens M; Fukunaga N; Davidson B; Dick J E; +
TI A recombinant bcl-x s **adenovirus** selectively **induces apoptosis** in cancer cells but not in normal bone marrow cells.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Nov 21) 92 (24) 11024-8.
Journal code: 7505876. ISSN: 0027-8424.

L6 ANSWER 280 OF 308 MEDLINE DUPLICATE 164
AU Zhu H; Shen Y; Shenk T
TI Human cytomegalovirus IE1 and IE2 proteins block apoptosis.
SO JOURNAL OF VIROLOGY, (1995 Dec) 69 (12) 7960-70.
Journal code: 0113724. ISSN: 0022-538X.

L6 ANSWER 281 OF 308 MEDLINE DUPLICATE 165
AU Lin H J; Eviner V; Prendergast G C; White E
TI Activated H-ras rescues E1A-induced apoptosis and cooperates with E1A to overcome p53-dependent growth arrest.
SO MOLECULAR AND CELLULAR BIOLOGY, (1995 Aug) 15 (8) 4536-44.
Journal code: 8109087. ISSN: 0270-7306.

L6 ANSWER 282 OF 308 MEDLINE DUPLICATE 166
AU Yang C; Cirielli C; Capogrossi M C; Passaniti A
TI **Adenovirus**-mediated wild-type p53 expression **induces apoptosis** and suppresses tumorigenesis of prostatic tumor cells.
SO CANCER RESEARCH, (1995 Oct 1) 55 (19) 4210-3.
Journal code: 2984705R. ISSN: 0008-5472.

L6 ANSWER 283 OF 308 MEDLINE DUPLICATE 167
AU Pan H; Griep A E
TI Temporally distinct patterns of p53-dependent and p53-independent

apoptosis during mouse lens development.
SO GENES AND DEVELOPMENT, (1995 Sep 1) 9 (17) 2157-69.
Journal code: 8711660. ISSN: 0890-9369.

L6 ANSWER 284 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Sawada, Makoto
TI Apoptosis-regulating factors which bind adenovirus E1A and E1B proteins
SO Jikken Igaku (1995), 13(16), 1884-9
CODEN: JIIGEF; ISSN: 0288-5514

L6 ANSWER 285 OF 308 MEDLINE DUPLICATE 168
AU Voelkel-Johnson C; Entingh A J; Wold W S; Gooding L R; Laster S M
TI Activation of intracellular proteases is an early event in TNF-induced apoptosis.
SO JOURNAL OF IMMUNOLOGY, (1995 Feb 15) 154 (4) 1707-16.
Journal code: 2985117R. ISSN: 0022-1767.

L6 ANSWER 286 OF 308 MEDLINE DUPLICATE 169
AU Bennett M R; Gibson D F; Schwartz S M; Tait J F
TI Binding and phagocytosis of apoptotic vascular smooth muscle cells is mediated in part by exposure of phosphatidylserine.
SO CIRCULATION RESEARCH, (1995 Dec) 77 (6) 1136-42.
Journal code: 0047103. ISSN: 0009-7330.

L6 ANSWER 287 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Shisler, J. (1); Duerksen-Hughes, P.; Gooding, L. R.; Hermiston, T.; Wold,
W.s. M.
TI **Adenovirus** E1A **induces** susceptibility to TNF-**induced apoptosis** via its interaction with either pRB or p300.
SO 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 800. The 9th International Congress of Immunology.
Publisher: 9th International Congress of Immunology San Francisco, California, USA.
Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995

L6 ANSWER 288 OF 308 MEDLINE DUPLICATE 170
AU Farrow S N; White J H; Martinou I; Raven T; Pun K T; Grinham C J; Martinou
J C; Brown R
TI Cloning of a bcl-2 homologue by interaction with adenovirus E1B 19K.
SO NATURE, (1995 Apr 20) 374 (6524) 731-3.
Journal code: 0410462. ISSN: 0028-0836.

L6 ANSWER 289 OF 308 MEDLINE DUPLICATE 171
AU Ink B S; Gilbert C S; Evan G I
TI Delay of vaccinia virus-induced apoptosis in nonpermissive Chinese hamster
ovary cells by the cowpox virus CHOhr and adenovirus E1B 19K genes.
SO JOURNAL OF VIROLOGY, (1995 Feb) 69 (2) 661-8.
Journal code: 0113724. ISSN: 0022-538X.

L6 ANSWER 290 OF 308 MEDLINE DUPLICATE 172
AU Nakajima T; Ohi N; Arai T; Nozaki N; Kikuchi A; Oda K
TI **Adenovirus** E1A-**induced apoptosis** elicits a steep decrease in the topoisomerase II alpha level during the latent phase.

SO ONCOGENE, (1995 Feb 16) 10 (4) 651-62.
Journal code: 8711562. ISSN: 0950-9232.

L6 ANSWER 291 OF 308 MEDLINE DUPLICATE 173
AU Teodoro J G; Shore G C; Branton P E
TI **Adenovirus** E1A proteins **induce apoptosis** by both p53-dependent and p53-independent mechanisms.
SO ONCOGENE, (1995 Aug 3) 11 (3) 467-74.
Journal code: 8711562. ISSN: 0950-9232.

L6 ANSWER 292 OF 308 MEDLINE DUPLICATE 174
AU Grand R J; Milner A E; Mustoe T; Johnson G D; Owen D; Grant M L; Gregory C
D
TI A novel protein expressed in mammalian cells undergoing apoptosis.
SO EXPERIMENTAL CELL RESEARCH, (1995 Jun) 218 (2) 439-51.
Journal code: 0373226. ISSN: 0014-4827.

L6 ANSWER 293 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Cirielli, C. (1); Pili, R.; Gloe, T. R. (1); Chang, J.; Inyaku, K. (1); Passaniti, A.; Capogrossi, M. C.
TI **Adenovirus**-mediated gene transfer of wild-type p53 **induces** melanoma cell **apoptosis** in vitro and tumor growth inhibition in vivo.
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 421.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for
Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X.

L6 ANSWER 294 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Liu, T.-J.; McDonnell, T. J.; Teague, K. D.; El-Naggar, A. K.; Wang, M.; Clayman, G. L.
TI **Induction** of **apoptosis** by wild-type p53 **adenovirus** in head and neck squamous cell carcinoma.
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 415.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for
Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X.

L6 ANSWER 295 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 175
AU Shisler, J. (1); Duerksen-Hughes, P.; Gooding, L. R.; Hermiston, T.; Wold,
W. S. M.
TI **Adenovirus** E1A **induces** susceptibility to TNF-**induced apoptosis** via its interaction with either pRB or p300.
SO FASEB Journal, (1995) Vol. 9, No. 3, pp. A243.
Meeting Info.: Experimental Biology 95, Part I Atlanta, Georgia, USA April
9-13, 1995
ISSN: 0892-6638.

L6 ANSWER 296 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Subramanian, T.; Tarodi, Bela; Chinnadurai, G.
TI p53-independent apoptotic and necrotic cell deaths induced by adenovirus

infection: suppression by E1B 19K and Bcl-2 proteins
SO Cell Growth Differ. (1995), 6(2), 131-7
CODEN: CGDIE7; ISSN: 1044-9523

L6 ANSWER 297 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Chen, Gang; Branton, Philip E.; Shore, Gordon C.
TI Induction of p53-independent apoptosis by hygromycin B: suppression by Bcl-2 and adenovirus E1B 19-kDa protein
SO Experimental Cell Research (1995), 221(1), 55-9
CODEN: ECREAL; ISSN: 0014-4827

L6 ANSWER 298 OF 308 CAPLUS COPYRIGHT 2002 ACS
IN Perricaudet, Michel; Haddada, Hedi; May, Evelyne
TI Integration-defective adenoviruses carrying tumor suppressor or lymphokine genes for gene therapy of tumors
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2

L6 ANSWER 299 OF 308 MEDLINE DUPLICATE 176
AU Chiou S K; Tseng C C; Rao L; White E
TI Functional complementation of the adenovirus E1B 19-kilodalton protein with Bcl-2 in the inhibition of apoptosis in infected cells.
SO JOURNAL OF VIROLOGY, (1994 Oct) 68 (10) 6553-66.
Journal code: 0113724. ISSN: 0022-538X.

L6 ANSWER 300 OF 308 MEDLINE DUPLICATE 177
AU Chiou S K; Rao L; White E
TI Bcl-2 blocks p53-dependent apoptosis.
SO MOLECULAR AND CELLULAR BIOLOGY, (1994 Apr) 14 (4) 2556-63.
Journal code: 8109087. ISSN: 0270-7306.

L6 ANSWER 301 OF 308 MEDLINE DUPLICATE 178
AU Mymryk J S; Shire K; Bayley S T
TI **Induction** of **apoptosis** by **adenovirus** type 5 E1A in rat cells requires a proliferation block.
SO ONCOGENE, (1994 Apr) 9 (4) 1187-93.
Journal code: 8711562. ISSN: 0950-9232.

L6 ANSWER 302 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU White, E.; Chiou, S. -K.; Rao, L.; Sabbatini, P.; Lin, H. -J.
TI Control of p53-dependent apoptosis by E1B, Bcl-2, and Ha-ras proteins
SO Cold Spring Harbor Symp. Quant. Biol. (1994), 59(Molecular Genetics of Cancer), 395-402
CODEN: CSHSAZ; ISSN: 0091-7451

L6 ANSWER 303 OF 308 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Shisler, J. (1); Duerksen-Hughes, P. (1); Hermiston, T.; Wold, W. S. M.; Gooding, L. R. (1)
TI **Adenovirus** E1A **induces** cellular sensitivity to TNF-**induced apoptosis** via its interaction within either Rb or P300.
SO European Cytokine Network, (1994) Vol. 5, No. 2, pp. 115.
Meeting Info.: 5th International Congress on Tumor Necrosis Factor Monterey, California, USA May 30-June 3, 1994
ISSN: 1148-5493.

L6 ANSWER 304 OF 308 MEDLINE DUPLICATE 179
AU Lowe S W; Ruley H E; Jacks T; Housman D E
TI p53-dependent apoptosis modulates the cytotoxicity of anticancer agents.

SO CELL, (1993 Sep 24) 74 (6) 957-67.
Journal code: 0413066. ISSN: 0092-8674.

L6 ANSWER 305 OF 308 CAPLUS COPYRIGHT 2002 ACS
AU Debbas, Michael; White, Eileen
TI Wild-type p53 mediates apoptosis by E1A, which is inhibited by E1B
SO Genes Dev. (1993), 7(4), 546-54
CODEN: GEDEEP; ISSN: 0890-9369

L6 ANSWER 306 OF 308 MEDLINE DUPLICATE 180
AU Lowe S W; Ruley H E
TI Stabilization of the p53 tumor suppressor is **induced** by **adenovirus** 5 E1A and accompanies **apoptosis**.
SO GENES AND DEVELOPMENT, (1993 Apr) 7 (4) 535-45.
Journal code: 8711660. ISSN: 0890-9369.

L6 ANSWER 307 OF 308 MEDLINE DUPLICATE 181
AU Wold W S
TI Adenovirus genes that modulate the sensitivity of virus-infected cells to lysis by TNF.
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1993 Dec) 53 (4) 329-35. Ref: 28
Journal code: 8205768. ISSN: 0730-2312.

L6 ANSWER 308 OF 308 MEDLINE DUPLICATE 182
AU Rao L; Debbas M; Sabbatini P; Hockenbery D; Korsmeyer S; White E
TI The **adenovirus** E1A proteins **induce apoptosis**, which is inhibited by the E1B 19-kDa and Bcl-2 proteins.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Aug 15) 89 (16) 7742-6.
Journal code: 7505876. ISSN: 0027-8424.

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=> d his

(FILE 'HOME' ENTERED AT 17:08:24 ON 14 AUG 2002)

FILE 'MEDLINE, CAPLUS, SCISEARCH, BIOSIS' ENTERED AT 17:08:45 ON 14 AUG 2002

L1 22506 S RETROVIR?(2A)VECTOR
L2 877 S COMPLEMENT?(W)CELL
L3 23 S L1 AND L2
L4 10 DUP REM L3 (13 DUPLICATES REMOVED)

=> d au ti so ab 1-10 l4

L4 ANSWER 1 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)
AU Mizuguchi H (Reprint); Kay M A; Hayakawa T
TI Approaches for generating recombinant adenovirus vectors
SO ADVANCED DRUG DELIVERY REVIEWS, (19 NOV 2001) Vol. 52, No. 3, pp. 165-176.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0169-409X.
AB Various methods have been developed to facilitate the generation of recombinant adenovirus vectors, and three commercially available methods have been most widely used: the homologous recombination method in E1-**complement cell** lines, the homologous recombination method in bacteria, and an in vitro ligation method based on simple routine plasmid construction. These methods can insert foreign genes not only into the E1 deletion region, but also into the E3 deletion region, thereby permitting the construction of a binary transgene expression system in which heterologous genes can be inserted into both the E1 and E3 regions. By modifying the latter two methods, fiber-mutant adenovirus vectors can be also constructed in order to modify vector tropism. In this paper, we review recent advances in the construction of first generation adenovirus vectors and fiber-modified adenovirus vectors. (C) 2001 Elsevier Science B.V. All rights reserved.

L4 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
AU Prichard M N; Gao N; Jairath S; Mulamba G; Krosky P; Coen D M; Parker B O; Pari G S
TI A recombinant human cytomegalovirus with a large deletion in UL97 has a severe replication deficiency.
SO JOURNAL OF VIROLOGY, (1999 Jul) 73 (7) 5663-70.
Journal code: 0113724. ISSN: 0022-538X.
AB Human cytomegalovirus encodes a protein kinase (UL97) that confers sensitivity to ganciclovir by phosphorylating it to the monophosphate. The function of this unusual kinase in viral replication is unknown. We constructed two independent isolates of a recombinant virus, RCDelta97, that contain large deletions in this gene and carry a 4.8-kb insertion containing a selectable genetic marker. These mutant viruses were isolated by using a population of primary cells (HEL97) that express this gene from integrated copies of a defective **retroviral vector**. The recombinant viruses were severely impaired in their ability to replicate in primary fibroblasts, attaining virus titers that were 2 to 3

orders of magnitude lower than those produced by the parent virus. Despite the severe replication deficit, both of these viruses retained the ability to form small, slowly growing plaques in primary fibroblasts, demonstrating that UL97 is not absolutely essential for replication in cell culture. The replication deficit was relieved when UL97 was provided in trans in the **complementing cell** line, showing that the phenotype was due to a deficiency in UL97. Thus, the UL97 gene product plays a very important role in viral replication in tissue culture and may be a good target for antiviral chemotherapy.

L4 ANSWER 3 OF 10 MEDLINE DUPLICATE 2
AU Benedict C A; Tun R Y; Rubinstein D B; Guillaume T; Cannon P M; Anderson W F
TI Targeting **retroviral vectors** to CD34-expressing cells: binding to CD34 does not catalyze virus-cell fusion.
SO HUMAN GENE THERAPY, (1999 Mar 1) 10 (4) 545-57.
Journal code: 9008950. ISSN: 1043-0342.
AB We have attempted to engineer murine leukemia virus (MuLV)-based **retroviral vectors** to specifically transduce cells expressing human CD34, an antigen present on the surface of undifferentiated hematopoietic stem cells. A number of chimeric ecotropic MuLV envelope (Env) proteins were constructed that contained anti-CD34 single-chain antibody variable fragments (scFvs). The scFv-Env proteins were generated either by replacing the receptor-binding domain of Env with the scFv or by inserting the scFv into the N terminus of the Env protein. Only chimeric Env proteins with scFv insertions between amino acids 6 and 7 were incorporated into viral particles, and coexpression of native MuLV Env did not rescue incorporation-defective proteins. In addition, the efficiency of incorporation varied with the specific anti-CD34 scFv that was used. **Retroviral vectors** containing the scFv-Env proteins bound to CD34+ cells and transduced NIH 3T3 cells expressing human CD34 (3T3-CD34 cells) at approximately twice the efficiency of the parental NIH 3T3 cells. However, the introduction of the mutation D84K, which prevents binding to the ecotropic MuLV receptor mcat-1, prevented transduction of both NIH 3T3 and 3T3-CD34 cells. **Complementation cell**-cell fusion assays [Zhao et al. (1997). J. Virol. 71, 6967-6972] in 3T3-CD34 cells revealed that although the scFv-Env proteins could contribute postbinding entry functions when bound to mcat-1, they were unable to do so when bound to CD34. Taken together, these data suggest that although the interaction with CD34 effectively increased the concentration of virus on 3T3-CD34 cells, entry could occur only through an interaction with mcat-1; CD34 alone was not capable of triggering the appropriate postbinding changes that lead to viral entry.

L4 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS
AU Dumaz, Nicolas; Drougard, Christiane; Quilliet, Xavier; Mezzina, Mauro; Sarasin, Alain; Daya-Grosjean, Leela
TI Recovery of the normal p53 response after UV treatment in DNA repair-deficient fibroblasts by retroviral-mediated correction with the XPD gene
SO Carcinogenesis (1998), 19(9), 1701-1704
CODEN: CRNGDP; ISSN: 0143-3334
AB Among the major responses of human cells to DNA damage is accumulation of the p53 tumor suppressor protein, which plays a crucial role as a

cell-cycle checkpoint. We have already shown that this response is different in cells from the UV-hypersensitive human syndromes xeroderma pigmentosum (XP) and trichothiodystrophy (TTD), which overlap with each other and arise from mutations in genes involved in nucleotide excision repair. In this paper we report that correction of the repair defect by retroviral-mediated transduction of the wild-type XPD gene in XP-D and TTD/XP-D untransformed primary fibroblasts leads to a normal p53 response in these cells. Thus, the **complemented cells**, like normal human fibroblasts, require higher UV doses (10 J/m2) for p53 induction than the parental repair-deficient XP-D or TTD/XP-D cells (both mapping at the XPD locus), which accumulate p53 protein at very low UV doses (2.5 and 5 J/m2). The p53 protein levels return to normal 24 h after irradn. when UV-induced lesions have been efficiently repaired by the restored NER activity. These data confirm our earlier results that p53 accumulation following UV treatment is directly related to the presence of unrepaired cyclobutane dimers on the transcribed strand of active genes.

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS
IN Lusky, Monika; Mehtali, Majid
TI Helper viruses containing recombination sites flanking a gene necessary for viral propagation and their use for preparing recombinant replication-deficient viral vectors
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
AB Novel helper vectors are provided for complementing defective recombinant viral vectors, characterized in that they are provided with recombination sequences recognized by a recombinase. A **complementation cell** expressing the recombinase, and a method for prepg. recombinant viral vectors as infectious viral particles for transferring and expressing genes of interest in a host organism or cell, are also provided. THe invention is particularly suitable for use in gene therapy, esp. in humans. Adenoviral vector pTG4707 contg. an encapsidation signal flanked by loxP sites and lacking genes E1, E3 and E4 was constructed. **Complementing cells** 293/CRE-ER, which are 293 cells transformed with a plasmid expressing an estradiol receptor-Cre recombinase fusion protein were also prepd. 293/CRE-ER cells transfected with pTG4707 and an E4-contg. **retroviral vector** are cultured to produce a mixed population of viral particles. Estradiol is then introduced into the medium to activate the Cre recombinase and inhibit formation of viral particles. Viral vectors enriched in the desired vectors, i.e. contg. fewer helper viruses relative to prior art viral vector prepns., are obtained.

L4 ANSWER 6 OF 10 MEDLINE DUPLICATE 3
AU Quilliet X; Chevallier-Lagente O; Eveno E; Stojkovic T; Destee A; Sarasin A; Mezzina M
TI Long-term complementation of DNA repair deficient human primary fibroblasts by retroviral transduction of the XPD gene.
SO MUTATION RESEARCH, (1996 Dec 2) 364 (3) 161-9.
Journal code: 0400763. ISSN: 0027-5107.
AB Due to their limited life time in culture and their relative resistance to DNA transfection, primary fibroblasts derived from UV-hypersensitive patients could not be used for cloning DNA repair gene and studying stable complementation with wild-type DNA repair genes. Primary cells were only used for complementation analysis after transient expression through cell fusion. DNA microinjection and transfection. We report the

retroviral-mediated highly efficient transfer and stable expression of XPD/ERCC2 gene in fibroblast strains from eight different patients using the LXPDSN **retroviral vector**. Cells derived from skin biopsies of xeroderma pigmentosum and trichothiodystrophy patients were incubated with vector-containing suspension and selected with the neomycin-analog G418. LXPDSN vector specifically **complemented cells** belonging to the XP-D group. Long-term reversion of repair-deficient phenotype, monitored by UV survival and UDS analysis, has been achieved in these diploid fibroblasts. We demonstrate this methodology is a powerful tool to study phenotypic reversion of nucleotide excision repair-deficient cells such as cellular DNA repair properties and we suggest that it may be used to study other cellular parameters (cell cycle regulation, p53 stability or immunosurveillance-controlling factors) involved in UV-induced skin cancers and which reliability requires the use of untransformed cells.

L4 ANSWER 7 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)
AU IMLER J L; CHARTIER C; DREYER D; DIETERLE A; SAINTEMARIE M; FAURE T; PAVIRANI A; MEHTALI M (Reprint)
TI NOVEL **COMPLEMENTATION CELL**-LINES DERIVED FROM HUMAN LUNG-CARCINOMA A549 CELLS SUPPORT THE GROWTH OF E1-DELETED ADENOVIRUS VECTORS
SO GENE THERAPY, (JAN 1996) Vol. 3, No. 1, pp. 75-84.
ISSN: 0969-7128.
AB Replication-defective E1-deleted adenoviruses are attractive vectors for gene therapy or live vaccines. However, manufacturing methods required for their pharmaceutical development are not optimized. For example, the generation of E1-deleted adenovirus vectors relies on the complementation functions present in 293 cells. However, 293 cells are prone to the generation of replication competent particles as a result of recombination events between the viral DNA and the integrated adenovirus sequences present in the cell line. We report here that human lung A549 cells transformed with constitutive or inducible E1-expression vectors support the replication of E1-deficient adenoviruses. E1A transcription was elevated in most of the cell lines, and E1A proteins were expressed at levels similar to those of 293 cells. However, the levels of expression of E1A did not correlate with the efficiencies of complementation of E1-deleted viruses in A549 clones, since some clones complemented replication in the absence of induction of E1A expression. In addition, complementation of E1-deficient adenoviruses did not require expression of the E1B 55-kDa protein. Although these cell lines contain the coding and cis-acting regulatory sequences of the structural protein IX gene, they are not able to complement viruses in which this gene has been deleted. In contrast to 293 cells, such new **complementation cell** lines do not contain the left end of the adenoviral genome and thus represent a significant improvement over the currently used 293 cells, in which a single recombination event is sufficient to yield replication competent adenovirus.

L4 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

AU Mehtali, M.
TI **Complementation cell** lines for viral vectors to be used in gene therapy
SO Cytotechnology (1996), Volume Date 1995-1996, 19(1), 43-54
CODEN: CYTOER; ISSN: 0920-9069
AB A review, with 56 refs. Viral vectors provide a highly efficient method for the transfer of foreign genes into a variety of quiescent or dividing eukaryotic cells from many animal origins. While recombinant vectors derived from an increasing no. of mammalian viruses (herpes simplex virus, autonomous and non-autonomous parvoviruses, poxviruses, retroviruses, adenoviruses) are available today, vectors based on murine retroviruses and human adenoviruses constitute preferential candidates for the delivery of marker or therapeutic genes into human somatic cells. The availability of such vectors has made possible the recent transition of human gene therapy from lab. benches to clin. settings. Most current recombinant vectors have been generated by deleting essential viral genes in order to make space available for the introduction of passenger genes. Such vectors are therefore unable to replicate in the absence of these crit. gene products and their prodn. relies on the development of stable **complementation cell** lines providing in trans the missing viral functions. Although complementation (or packaging) cell lines are available for both adenovirus and **retrovirus vectors**, their resp. drawbacks still limit their use to research applications and phase I clin. trials. The future success or failure of human gene therapy will therefore rely on the prodn. of improved generations of packaging cell lines that can produce safer and more efficient vectors which are fully adapted to large scale prodn. and clin. applications.

L4 ANSWER 9 OF 10 MEDLINE DUPLICATE 5
AU Nouvel P; Panthier J J; Condamine H
TI The spread of a replication-competent MuLV **retroviral vector** can be efficiently blocked by deletion variants.
SO VIROLOGY, (1994 Oct) 204 (1) 180-9.
Journal code: 0110674. ISSN: 0042-6822.
AB A **retroviral vector** in which the gag and pol genes have been replaced by the NLS-lacZ reporter gene was derived from a cloned AKV-like virus. A **complementing cell** line expressing the gag and pol retroviral genes was constructed. The **retroviral vector** was demonstrated to replicate in the **complementing cells**. Since transfection is known to generate deletion variants of the introduced plasmid, we have examined whether it can give rise to viral forms with a replicating advantage over the initial vector. After transfection in **complementing cells** the spread of the vector was followed by X-gal staining. The fraction of stained cells increased for the first 10 days following transfection and was then stabilized to about 20% stained cells, thus defining two cell types; one with LacZ+ phenotype and one with LacZ- phenotype. Molecular analysis showed that the latter contains a deleted form of the virus preventing cell infection by the vector presumably through a mechanism of interference involving the viral env gene. Thus, interference results in the efficient block of vector expansion.

L4 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU Mehtali, M.
TI **Complementation cell** lines for viral vectors to be

used in gene therapy.
SO Cytotechnology, Vol. 19, No. 1, pp. 43-54.
ISSN: 0920-9069.
AB Viral vectors provide a highly efficient method for the transfer of foreign genes into a variety of quiescent or dividing eukaryotic cells from many animal origins. While recombinant vectors derived from an increasing number of mammalian viruses (herpes simplex virus, autonomous and non-autonomous parvoviruses, poxviruses, retroviruses, adenoviruses available today, vectors based on murine retroviruses and human adenoviruses constitute preferential candidates for the delivery of marker or therapeutic genes into human somatic cells. The availability of such vectors has made possible the recent transition of human gene therapy from laboratory benches to clinical settings. Most current recombinant vectors have been generated by deleting essential viral genes in order to make space available for the introduction of passenger genes. Such vectors are therefore unable to replicate in the absence of these critical gene products and their production relies on the development of stable **complementation cell** lines providing in trans the missing viral functions. Although complementation (or packaging) cell lines are available for both adenovirus and **retrovirus vectors**, their respective drawbacks still limit their use to research applications and phase I clinical trials. The future success or failure of human gene therapy will therefore rely on the production of improved generations of packaging cell lines that can produce safer and more efficient vectors which are fully adapted to large scale production and clinical applications.

=> d 5 bib l4

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS
AN 1997:211268 CAPLUS
DN 126:196099
TI Helper viruses containing recombination sites flanking a gene necessary for viral propagation and their use for preparing recombinant replication-deficient viral vectors
IN Lusky, Monika; Mehtali, Majid
PA Transgene S.A., Fr.; Lusky, Monika; Mehtali, Majid
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9705255	A2	19970213	WO 1996-FR1200	19960730
	WO 9705255	A3	19970306		
	W: AU, CA, JP, SG, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FR 2737501	A1	19970207	FR 1995-9289	19950731
	FR 2737501	B1	19971024		
	CA 2225551	AA	19970213	CA 1996-2225551	19960730
	AU 9667044	A1	19970226	AU 1996-67044	19960730
	AU 715487	B2	20000203		
	EP 842279	A2	19980520	EP 1996-927107	19960730
	EP 842279	B1	20011031		
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IE, FI

	JP 11510049	T2	19990907	JP 1996-507291	19960730
	EP 1132478	A2	20010912	EP 2001-108475	19960730
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	AT 207959	E	20011115	AT 1996-927107	19960730
	ES 2164910	T3	20020301	ES 1996-927107	19960730
	US 6066478	A	20000523	US 1998-11257	19980309
	US 6350575	B1	20020226	US 2000-563239	20000502
	US 2002072120	A1	20020613	US 2001-920932	20010803
PRAI	FR 1995-9289	A	19950731		
	EP 1996-927107	A3	19960730		
	WO 1996-FR1200	W	19960730		
	US 1998-11257	A1	19980309		
	US 2000-563239	A1	20000502		